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APPLICATION NUMBER: *60/531,957*
FILING DATE: *December 23, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/43082*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT und r 37 CFR 1.53(c).

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
James John Jeffrey	Pearson Talley	Cambridge, MA Somerville, MA

☐ *Additional inventors are being named on the ____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (280 characters max)

COMPOUNDS AND METHODS FOR THE TREATMENT OF ASTHMA

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* ~~48~~ 49

☐ Drawing(s) *Number of Sheets*

☒ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27.

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Respectfully submitted,

SIGNATURE

Date 12/23/03

REGISTRATION NO. *(if appropriate)* 32,700

Docket Number: 2221.008P

TYPED or PRINTED NAME Philip E. Hansen

TELEPHONE 518-452-5600

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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Applicant: Pearson et al.

Title: COMPOUNDS AND METHODS FOR THE TREATMENT OF ASTHMA

Attorney Docket No.: 2221.008P

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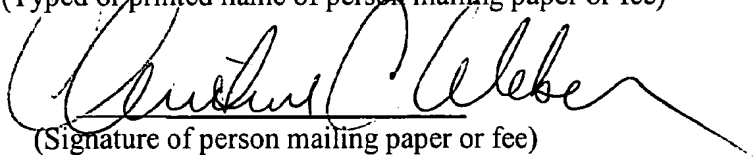

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COMPOUNDS AND METHODS FOR THE TREATMENT OF ASTHMA

Field of the Invention

[0001] The invention relates to compounds and methods for the treatment of asthma. The methods involve mast cell stabilization together with selective inhibition of iNOS. The compounds are combinations of a mast cell inhibiting moiety and an inhibitor of iNOS.

Background of the Invention

[0002] Asthma is a chronic airway inflammatory disorder characterized by bronchial hyper-reactivity and bronchospasm, among other abnormalities. Lungs of asthmatic patients have increased numbers of inflammatory cells in bronchioalveolar fluid and in lung tissues. These inflammatory cells include eosinophils, basophils, neutrophils, macrophages, and lymphocytes. In asthmatic lungs, the epithelium, including ciliated columnar epithelial cells, is damaged. IgE-antigen-mast cell interactions represent the early molecular and cellular events that cause inflammatory conditions of asthma.

[0003] Mast Cell Stabilizing Agents provide one approach to the prophylaxis/treatment of asthma. The prototype drug, disodium cromoglycate was synthesized in 1965 and was approved in the United States in 1973 as a prophylactic, nonbronchodilating anti-inflammatory drug for the therapy of allergic disorder. Cromolyn is an odorless, white, hygroscopic crystalline powder that is freely soluble in water up to 5%. Animal and human studies show it to be excreted unchanged in bile and urine. When inhaled into the pulmonary tree, as for treatment of asthma, only about 8% of a dose is deposited in the lung and absorbed. Peak plasma levels occur within 15 minutes, the biologic half-life is 46-99 minutes. Oral administration in humans results in approximately 1% being systemically absorbed. Cromolyn toxicity studies show an impressively low order of acute toxicity, and adverse effects tend to be minimal and reversible. Cromolyn has a unique, purely prophylactic action

with no intrinsic bronchodilator or antihistaminic activity. Nedocromil was introduced subsequent to cromolyn. It is the other standard mast cell stabilizer used in the treatment of asthma. Its chemical properties and therapeutic characteristics are similar.

[0004] Nitric oxide (NO) is a diffusible radical involved in many physiological and pathological processes. It is synthesized *in vivo* by oxidation of L-arginine. The synthesis is catalyzed by a family of enzymes known as nitric oxide synthases or NO-synthases (NOSs), which are referenced in the international enzyme nomenclature system under the number E.C.1.14.13.39. Three NOS isoforms, two of which are constitutive and one inducible, as known:
(1) A neuronal NOS (NOS-1 or nNOS) was originally isolated and cloned from nerve tissue in which it is a constitutive enzyme. nNOS produces NO in response to various physiological stimuli, such as the activation of membrane receptors, according to a mechanism dependent on calcium and on calmodulin. nNOS-derived NO serves as a neurotransmitter;
(2) An inducible NOS (NOS-2 or iNOS) can be induced in response to immunological stimuli such as, for example, cytokines or bacterial antigens in various cells such as, for example macrophages, epithelial cells, hepatocytes, glial cells, and other cell types. The activity of this isoform is not regulated by calcium. Once induced, it produces large amounts of NO over prolonged periods.
(3) An endothelial NOS (NOS-3 or eNOS) is constitutive and calcium/calmodulin-dependent. It was originally identified in vascular endothelial cells, in which it generates NO in response to physiological stimuli such as the activation of membrane receptors.

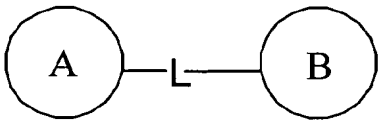
[0005] Nitric oxide produced by eNOS and nNOS plays a critical role in cellular signaling and acts to control numerous physiologic functions including vasodilation and bronchodilation in the lung. In the asthmatic lung, eNOS and nNOS are downregulated, and thus contribute to edema and bronchoconstriction. Contemplating the problem of inadequate eNOS and nNOS activity, in an approach which is the opposite of that taken in the present invention, Garvey et al. (US published application 2003/01995290) have attached stimulators of endogenous NO production to mast cell inhibitors.

[0006] The NO produced in large amounts by the inducible isoform iNOS is involved in pathological phenomena associated with acute and chronic inflammatory processes in a large variety of tissues and organs. NO is highly reactive and, together with superoxide, forms peroxynitrite which damages tissues. In asthma this results in epithelial cell extrusion, sloughing, and cessation of cilia function. An excessive production of NO by induction of iNOS thus plays a part in degenerative pathologies with inflammatory components, such as asthma.

[0007] In conditions in which an overproduction of NO is deleterious, it would be desirable to reduce the production of NO by administering substances capable of inhibiting iNOS. However, given the important physiological roles played by the constitutive isoforms, selective inhibition of iNOS is required.

Summary of the Invention

[0008] In a composition aspect, the invention relates to agents for treating a pulmonary disorder represented by the structure:



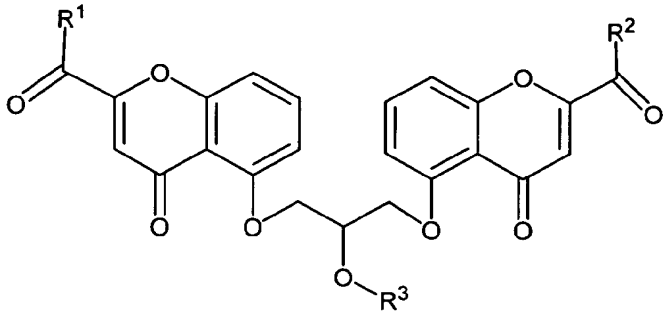
wherein

A is a mast-cell stabilizer;

L is a covalent linkage;

B is an iNOS inhibitor.

[0009] Examples of such agents are compounds of formula I or II



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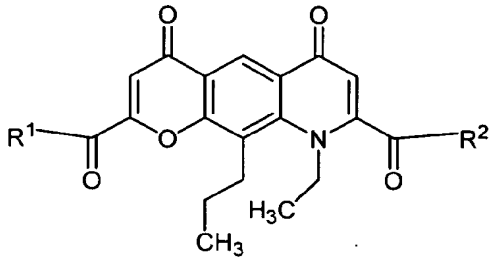


II

wherein

R^1 and R^2 are chosen from hydroxy, alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -O^- X^+, wherein X^+ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

-O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of iNOS;

R^5 is -O-R^{20}-U, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

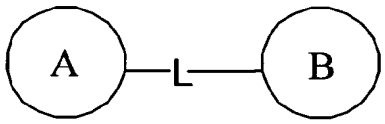
-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is an inhibitor of iNOS;

-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is an inhibitor of iNOS;

G is a linking moiety cleavable under physiologic conditions. In the compounds of the invention, at least one of R^1, R^2 and R^3 must be -G-O(C=O)R^4, -R^5, -NHR^6, -OR^7, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 or -(C=O)OR^7.

[0010] In another composition aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound as described above.

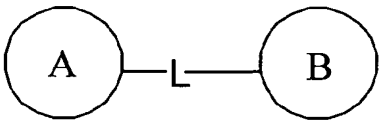
[0011] In a method aspect the invention relates to a method for treating a pulmonary disorder comprising administering a compound represented by the structure:



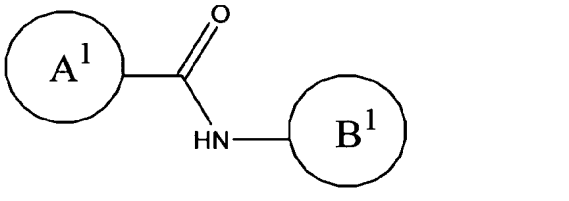
[0012] In a second method aspect, the invention relates to a method for treating a pulmonary disorder comprising co-administering a mast-cell stabilizer and an iNOS inhibitor in the form of a salt, in which one of the mast-cell stabilizer and the iNOS inhibitor is a cation or dication, and the other is an anion or dianion.

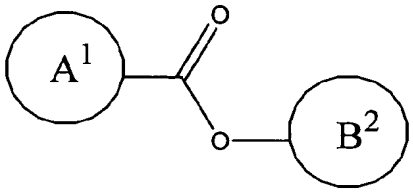
Detailed Description of the Invention

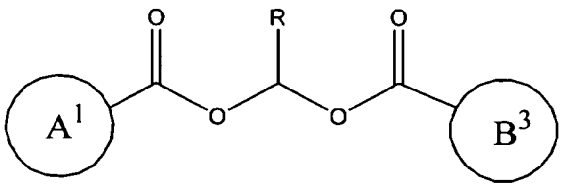
[0013] Agents for treating a pulmonary disorder according to the invention are represented by the structure:

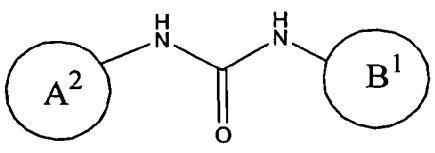


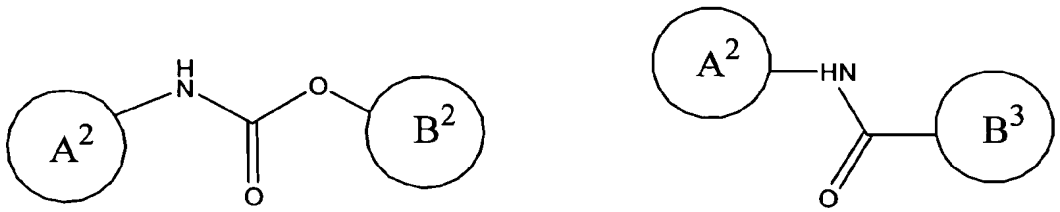
[0014] In one embodiment, L is chosen from -CONH-, -COO-, -O(C=O)O-, -O(C=O)NH-, -NHCONH- and -(C=O)OCH(R)O(C=O)- and the compound is represented by a structure chosen from:

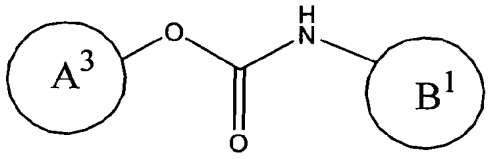


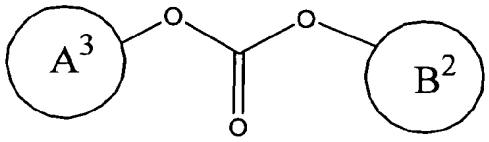


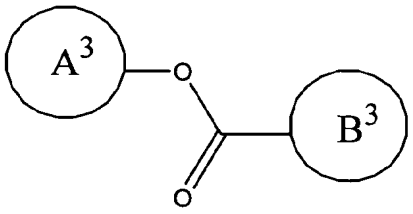








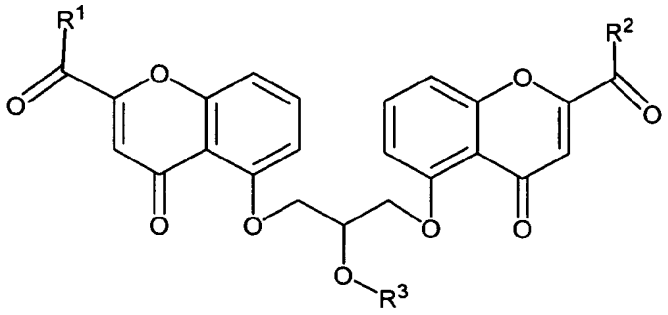




and

in which A^1 is a mast-cell stabilizer having a carboxylic acid substituent; A^2 is a mast-cell stabilizer having an amine substituent; A^3 is a mast-cell stabilizer having an alcohol substituent; B^1 is an iNOS inhibitor having an amine substituent; B^2 is an iNOS inhibitor having an alcohol substituent; B^3 is an iNOS inhibitor having a carboxylic acid substituent; and R is hydrogen or methyl. Cromolyn would be an example of a compound that fell into the categories A^1 (a mast-cell stabilizer having a carboxylic acid substituent) and A^3 (a mast-cell stabilizer having an alcohol substituent). Nedocromil would be an example of a compound that fell into category A^1. Numerous examples of compounds that fall in categories B^1, B^2 and B^3 are shown below as examples of parents of R^4.

[0015] In a particular embodiment, the compound is of formula I or II



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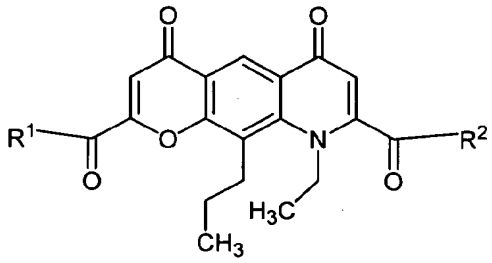


II

In these compounds

R^1 and R^2 are chosen from hydroxy, alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -$O^- X^+$, wherein X^+ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

-O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of iNOS;

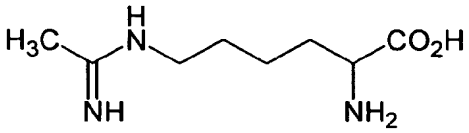
R^5 is -O-R^{20}-U, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

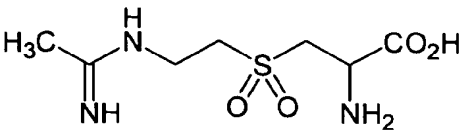
-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is an inhibitor of iNOS;

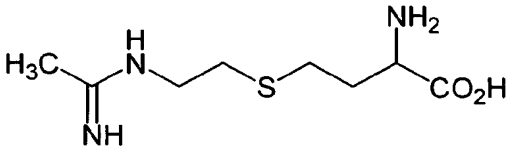
-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is an inhibitor of iNOS;

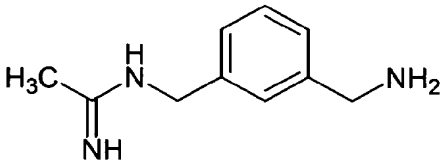
G is a linking moiety cleavable under physiologic conditions.

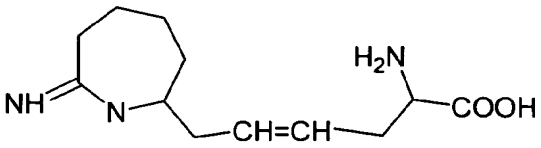
[0016] Preferred parents of the formulae R^4COOH and R^6NH_2 are chosen from:

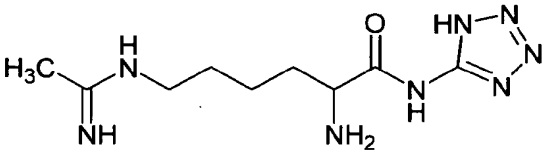


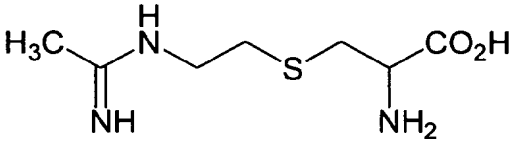


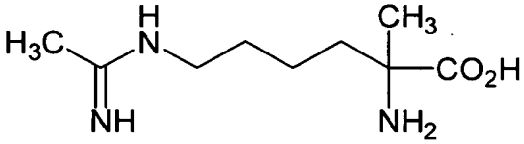


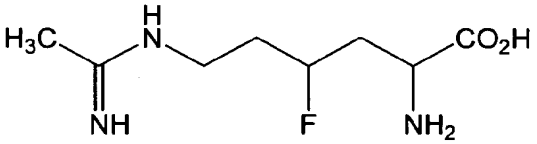


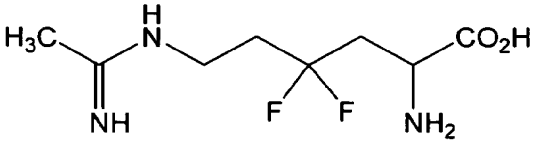


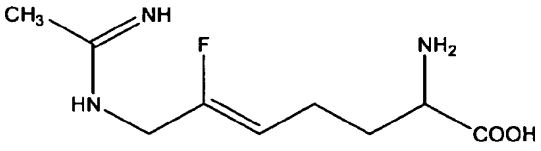


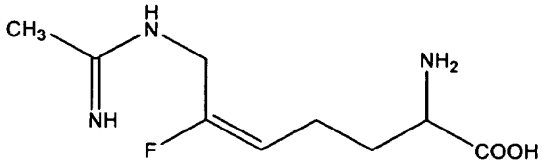


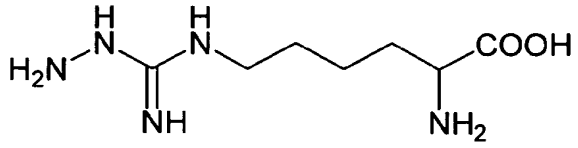




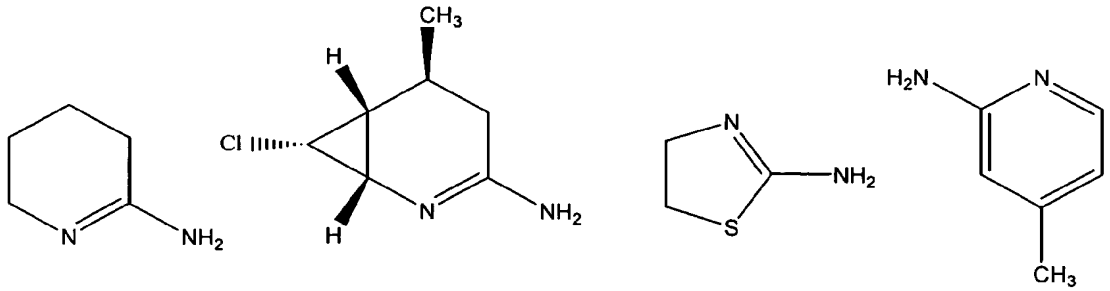


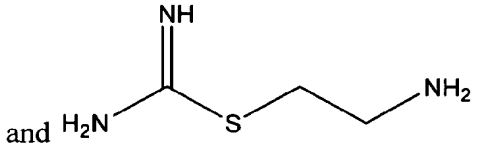




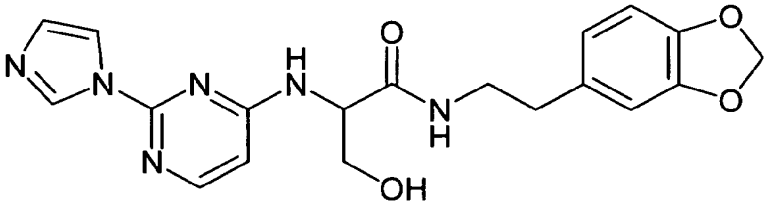
and 

Additional parents R^6NH_2 may be chosen from compounds of structure:

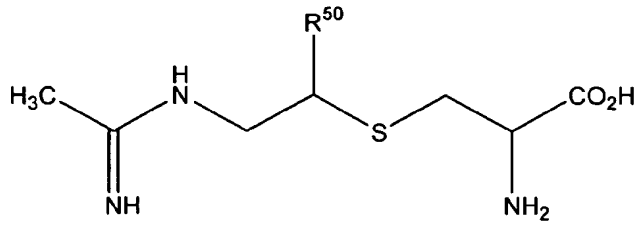


and 

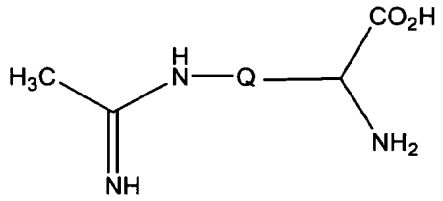
An exemplary parent of the formula R^7OH is the iNOS-inhibitory alcohol described in WO 98/37079 as example 53:



Additionally, parents of the formulae R^4COOH and R^6NH_2 are chosen from the iNOS inhibitors described in US pat 6,355,689:

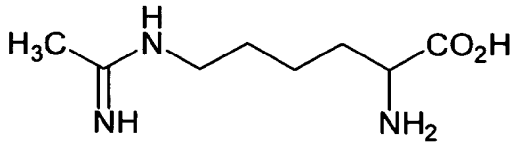


wherein R^{50} is chosen from C_1 to C_4 alkyl, C_3 to C_4 cycloalkyl, C_1 to C_4 hydroxyalkyl and C_1 to C_4 haloalkyl or US patent 5,863,931:



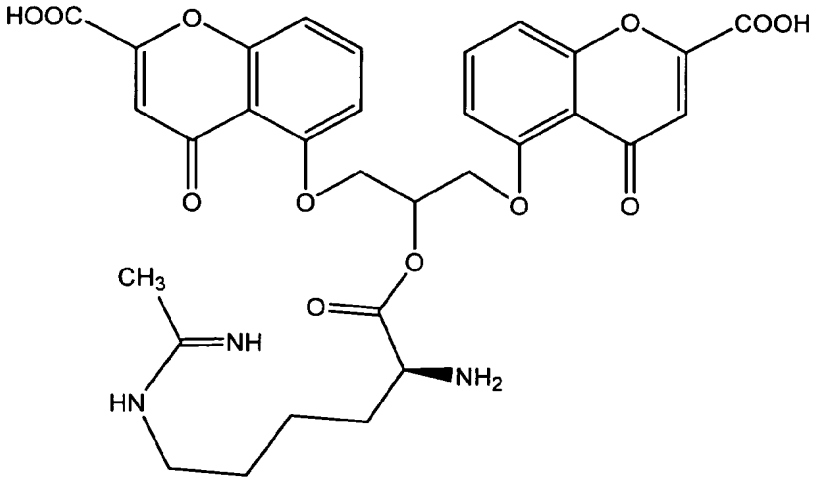
wherein Q is chosen from $-CH_2CH=CHCH_2-$, $-(CH_2)_pV(CH_2)_q-$, -O- , $-NR^{51}-$ and $-(CH_2)_rT(CH_2)_s-$; p is 2 or 3; q is 1 or 2; V is $S(O)_x$; x is 0, 1 or 2; R^{51} is H or C_{1-6} alkyl; r is 1 or 2; s is 1 or 2; and T is cyclobutyl, phenyl or pyridyl. Other iNOS inhibitors useful as parent structures in the instant invention may be found in US patents 6,451,821; 5,132,453; 5,830,917; 5,684,008; 6,207,708; 6,344,473; 6,143,790; 5,866,612; 6,369,272; 6,552,052; 6,495,544; 6,403,830; 5,629,322; 6,110,930; 6,228,866; 6,274,557; 6,432,947; 6,451,821; 5,449,688; 5,723,451; 5,854,251; 5,863,931; 5,889,056; 5,919,787; 5,945,408; 5,972,940; 5,981,511; 6,355,689; 6,423,705 and 6,465,686; in US published applications 20030013702; 20020037927; 20020049202; 20030119826; 20020022631; 20020198243; 20030064978; 20030195256; 20030207896 and 20030109522; in PCT applications WO01/78719; WO01/05748; WO96/35677; WO96/33175; WO96/15120; WO95/11014; WO95/11231; WO95/25717; WO95/24382; WO94/12165; WO94/14780; WO93/13055; WO02/076395; WO03/097163; WO03/097050; WO03/026638; WO00/13709; WO00/26195; WO00/61126; WO01/00195; WO01/58867; WO01/74351; WO01/94325; WO02/00648; WO02/50021; WO93/05775; WO95/13805; WO95/34534; WO96/15120; WO96/27593; WO98/02555; WO98/37079; WO99/26657; WO99/46240 and WO03/026668 and in European published applications EP0446699; EP1299365; EP765308; EP957087 and EP1282413. As indicated in paragraph [0041] below, the relevant disclosures of all are incorporated herein by reference.

[0017] The concept of "parent", as used herein, refers to a compound, such as **1**

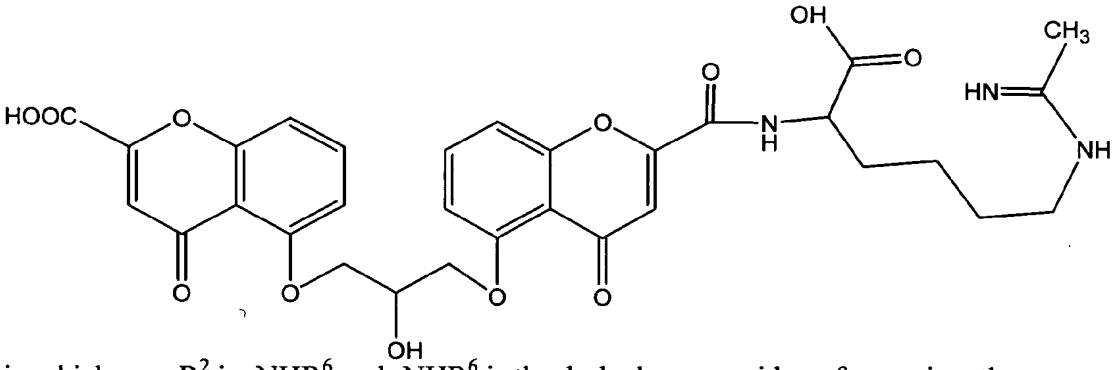


1

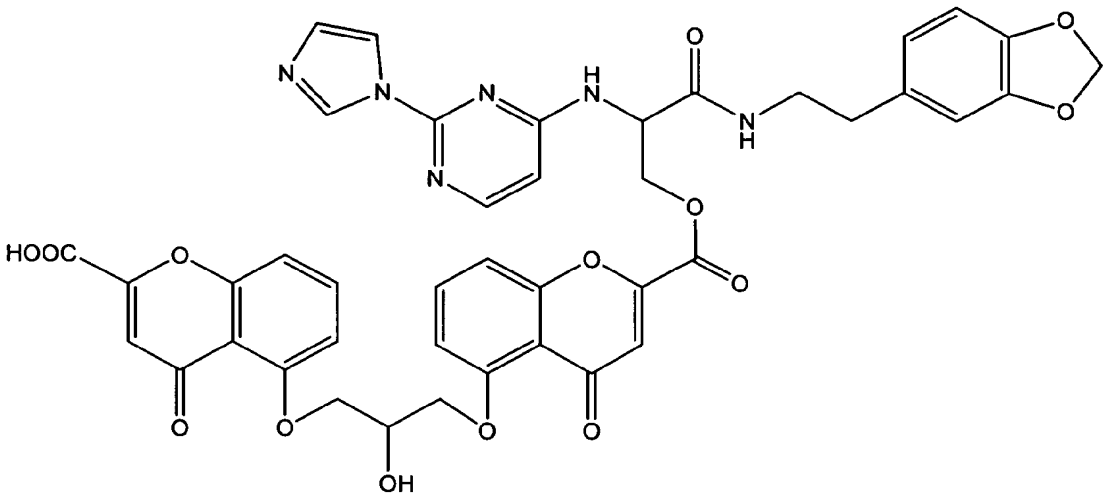
which is a selective inhibitor of iNOS. When the residue of this parent is attached to a chroman of formula I, one possible resulting structure is:



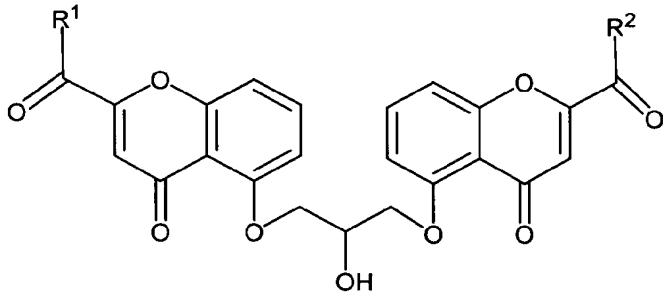
in which R^3 is -(C=O)R^4 and -(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, **1**, is an inhibitor of iNOS. It will be immediately apparent that **1** could also be attached to **I** as an amide:



in which case R^2 is -NHR^6 and -NHR^6 is the deshydrogen residue of an amine, the parent of which, **1**, is an inhibitor of iNOS. Similarly, alcohols may be attached as esters:



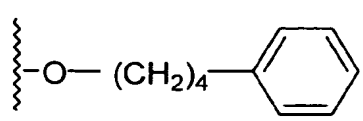
[0018] In one subgenus, R^1 and R^2 are chosen from hydroxy, alkoxy, $-R^5$, $-NHR^6$, $-OR^7$ and $-O^- X^+$; and R^3 is chosen from hydrogen, $-(C=O)R^4$, $-(C=O)R^5$, $-(C=O)NHR^6$ and $-(C=O)OR^7$. Another genus includes compounds of formula:



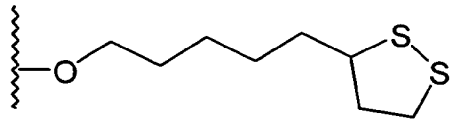
in which R^1 is chosen from $-G-O(C=O)R^4$, $-NHR^6$ and OR^7 ; and R^2 is chosen from hydroxy, alkoxy, R^5 and $-O^- X$..

[0019] In another subgenus at least one of R^1, R^2 and R^3 is $-G-O(C=O)R^4$ or $-(C=O)-G-O(C=O)R^4$; and G is chosen from $-OCH_2-$ and $-OCH(CH_3)-$. "G" in these cases forms an acetal of formaldehyde or acetaldehyde with the oxygen of $-O(C=O)R^4$. Acetals are particularly suitable as linkers that are readily cleaved under physiological conditions. Aminals also function as linkers that are readily cleaved under physiological conditions when the adjacent iNOS inhibitor is an amine.

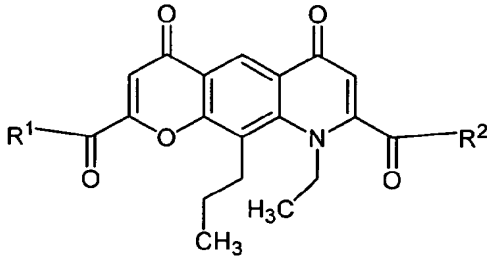
[0020] Preferred substituents R^5 are



and



In other subgenera the compounds are dioxo-4H,6H-pyrano[3,2-g]quinolines

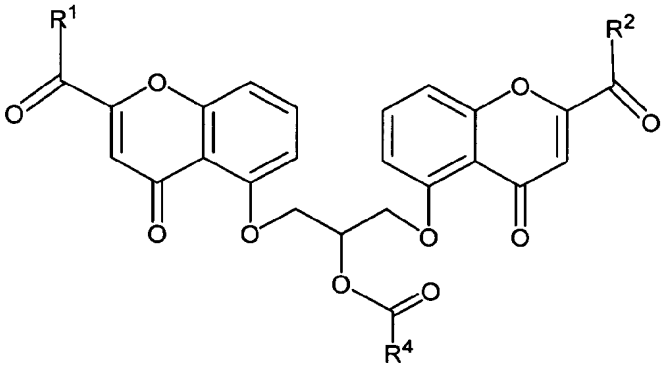


II

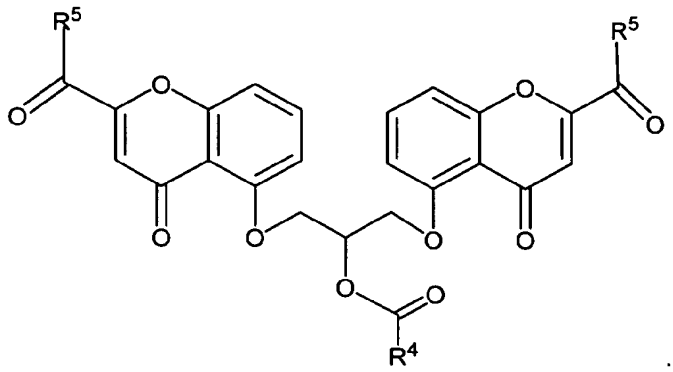
wherein R^1 is chosen from hydroxy, R^5 and $-O^- X$; and R^2 is chosen from -G-$O(C=O)R^4$, $-NHR^6$ and OR^7 or wherein R^1 is chosen from -G-$O(C=O)R^4$, $-NHR^6$ and OR^7 ; and

R^2 is chosen from hydroxy, R^5 and $-O^- X$.

[0021] Other subgenera include esters of formula



wherein R^1 and R^2 are chosen from hydroxy, alkoxy and $-O^- X^+$; and esters of formula



[0022] The compounds described herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. Each chiral center may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0023] The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr J. Chem. Ed. 62, 114-120 (1985): solid and broken wedges are used to denote the absolute configuration of a chiral element; wavy lines and single thin lines indicate disavowal of any stereochemical implication which the bond it represents could generate; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration.

[0024] The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration; thus a carbon-carbon double bond depicted arbitrarily herein as *E* may be *Z*, *E*, or a mixture of the two in any proportion.

[0025] As used herein, and as would be understood by the person of skill in the art, the recitation of "a compound" is intended to include salts and solvates of that compound.

[0026] The term "solvate" refers to a compound of Formula I in the solid state, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent for therapeutic administration is physiologically tolerable at the dosage administered. Examples of suitable solvents for therapeutic administration are ethanol and water. When water is the solvent, the solvate is referred to as a hydrate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions.

[0027] Compounds of formula I may contain basic or acidic residues, allowing them to be presented as salts. The term "pharmaceutically acceptable salt" refers to salts whose counter ion (anion) derives from pharmaceutically acceptable non-toxic acids and bases. When the compounds contain a quat or a basic residue, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include inorganic acids, organic acids and, in the case of quats, water (which formally furnishes the hydroxide anion). Examples include hydroxide, acetate, benzenesulfonate (besylate), benzoate, bicarbonate, bisulfate, carbonate, camphorsulfonate, citrate, ethanesulfonate, fumarate, gluconate, glutamate, bromide, chloride, isethionate, lactate, maleate, malate, mandelate, methanesulfonate, mucate, nitrate, pamoate, pantothenate, phosphate, succinate, sulfate, tartrate, p-toluenesulfonate, and the like. When the compounds contain an acidic residue, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

Definitions

[0028] Throughout this specification the terms and substituents retain their definitions.

[0029] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. Lower alkyl refers to alkyl groups of from 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s-and t-butyl and the like. Preferred alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like.

[0030] C_1 to C_{20} Hydrocarbon includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include benzyl, phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl.

[0031] Alkoxy or alkoxyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons.

[0032] Oxaalkyl refers to alkyl residues in which one or more carbons (and their associated hydrogens) have been replaced by oxygen. Examples include methoxypropoxy, 3,6,9-trioxadecyl and the like. The term oxaalkyl is intended as it is understood in the art [see Naming and Indexing of Chemical Substances for Chemical Abstracts, published by the American Chemical Society, ¶196, but without the restriction of ¶127(a)], i.e. it refers to compounds in which the oxygen is bonded via a single bond to its adjacent atoms (forming ether bonds). Similarly, thiaalkyl and azaalkyl refer to alkyl residues in which one or more carbons have been replaced by sulfur or nitrogen, respectively. Examples include ethylaminoethyl and methylthiopropyl.

[0033] Acyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof,

attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include formyl, acetyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzoyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

[0034] Aryl and heteroaryl mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-3 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S; or a tricyclic 13- or 14-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S. Aromatic 6- to 14-membered carbocyclic rings include, *e.g.,* benzene, naphthalene, indane, tetralin, and fluorene and the 5- to 10-membered aromatic heterocyclic rings include, *e.g.*, imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

[0035] Arylalkyl means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl and the like.

[0036] Substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein up to three H atoms in each residue are replaced with halogen, haloalkyl, hydroxy, loweralkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone, acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzyloxy, or heteroaryloxy.

[0037] The term "halogen" means fluorine, chlorine, bromine or iodine.

[0038] A "quaternary ammonium salt" as used herein refers to a substituent of the general formula - $N^+R^7R^8R^9$ X^-, in which R^7 is C_1 to C_{20} hydrocarbon or forms a five- to seven-membered ring with R^8; R^8 is alkyl or forms a five- to seven-membered ring with R^7; R^9 is alkyl or together with R^7 or R^8 forms a second five- to seven-membered ring; and X is an anion.

[0039] The term "prodrug" refers to a compound that is made more active *in vivo*. Commonly the conversion of prodrug to drug occurs by enzymatic processes in the liver or blood of the mammal. Many of the compounds of the invention may be chemically modified without absorption into the systemic circulation, and in those cases, activation *in vivo* may come about by chemical action (as in the acid-catalyzed cleavage of the acetals "G") or through the intermediacy of enzymes in the respiratory system, for example by esterases within the alveoli.

[0040] The terms "methods of treating or preventing" mean amelioration, prevention or relief from the symptoms and/or effects associated with lipid disorders. The term "preventing" as used herein refers to administering a medicament beforehand to forestall or obtund an acute episode. The person of ordinary skill in the medical art (to which the present method claims are directed) recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a
drug to substantially diminish the likelihood or seriousness of a condition, and this is the sense intended in applicants' claims. As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

[0041] Throughout this application, various references are referred to. The disclosures of these publications in their entireties are hereby incorporated by reference as if written herein.

[0042] The term "mammal" is used in its dictionary sense. Humans are included in the group of mammals, and humans would be the preferred subjects of the methods of treatment.

[0043] Terminology related to "protecting", "deprotecting" and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group which is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting

group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes of the invention, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups". Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as Protective Groups in Organic Synthesis by T.W.Greene [John Wiley & Sons, New York, 1991].

[0044] The abbreviations Me, Et, Ph, Tf, Ts and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, toluenesulfonyl and methanesulfonyl respectively. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations" is incorporated herein by reference.

[0045] The invention also encompasses pharmaceutical compositions comprising a pharmaceutically acceptable carrier and the foregoing compounds. Aerosol and oral pharmaceutical compositions are preferred. When oral, tablets, capsules and syrups are preferred.

[0046] While it may be possible for the compounds to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound as described above, or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0047] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The

formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0048] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0049] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein.

[0050] The pharmaceutical compositions may include a "pharmaceutically acceptable inert carrier", and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques, "Pharmaceutically acceptable carrier" also encompasses controlled release means.

[0051] Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must, of course, be compatible with the compound of the invention to

insure the stability of the formulation.

[0052] A preferred route for the administration of compounds of the present invention is inhalation. Formulations suitable for inhalation include sterile solutions for nebulization comprising a therapeutically effective amount of the compound dissolved in aqueous saline solution and optionally containing a preservative such as benzalkonium chloride or chlorobutanol, and aerosol formulations comprising a therapeutically effective amount dissolved or suspended in an appropriate propellant (e.g., HFA-134a, HFA-227, or a mixture thereof, or a chlorofluocarbon propellant such as a mixture of Propellants 11, 12, and/or 114) optionally containing a surfactant. Aerosols may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy. Also suitable are dry powder formulations comprising a therapeutically effective amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler.

[0053] Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container; these devices are likewise described in standard textbooks such as Sprowls and Remington.

[0054] The dose range for adult humans is generally from 0.005 mg to 10 g/day orally. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the

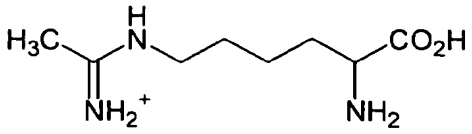
patient, the precise disorder being treated, and its severity.

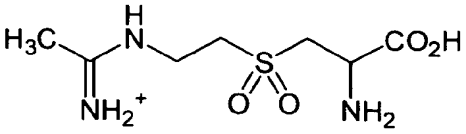
[0055] The invention also relates to methods for treating pulmonary disorders. According to the invention one may administer a compound as described above for treating bronchospasm, for inducing bronchodilation, for treating chronic obstructive pulmonary disease, for treating asthma and for treating rhinitis.

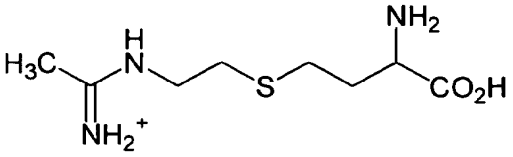
A broad spectrum of respiratory diseases and disorders have been recognized, many of which have overlapping and interacting etiologies. One of the most widespread and prevalent of these diseases in western populations is the chronic disease referred to as "asthma". Other such disorders are also characterized by acute pulmonary vasoconstriction such as may result from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post-cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, herapin-protamine reactions, sepsis, status asthmaticus or hypoxia (including iatrogenic hypoxia) and other forms of reversible pulmonary vasoconstriction. Such pulmonary disorders also are also characterized by inflammation of the lung including those associated with the migration into the lung of nonresident cell types including the various leucocyte subclasses. Also included in the respiratory disorders contemplated are cystic fibrosis and other diseases which are characterized by excess mucosal secretion. Other physiological events which are contemplated to be controlled include platelet activation in the lung.

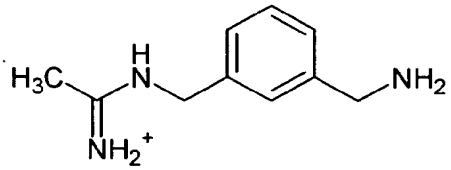
[0056] The methods for treating pulmonary disorders also encompass co-administering a mast-cell stabilizer and an iNOS inhibitor in the form of a salt, in which one of the mast-cell stabilizer and the iNOS inhibitor is a cation or dication, and the other is an anion or dianion.

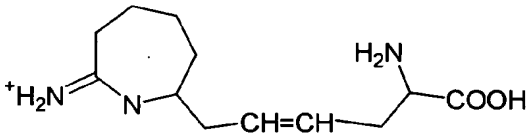
Exemplary cations include:

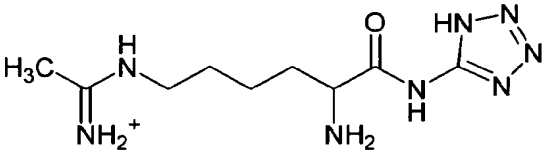


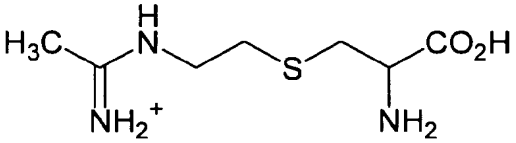


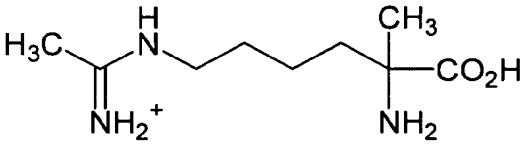


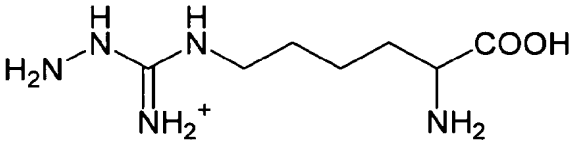


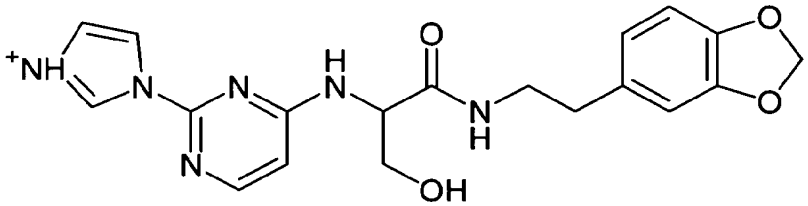


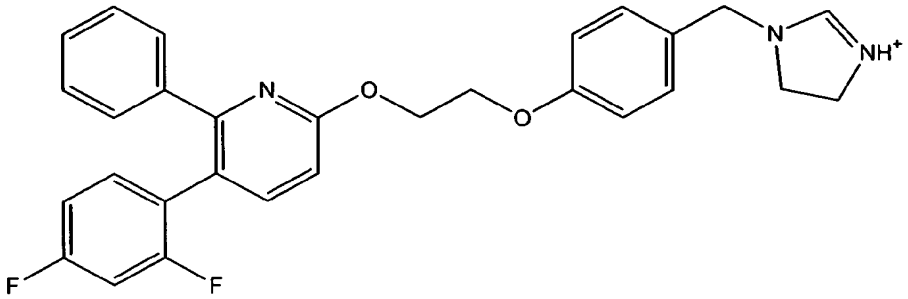
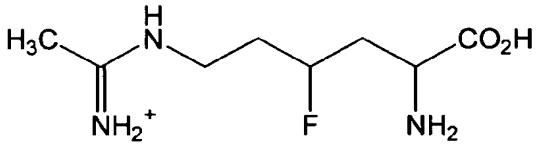
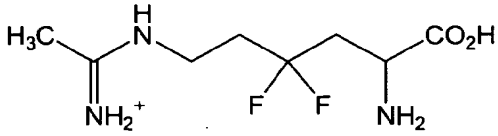
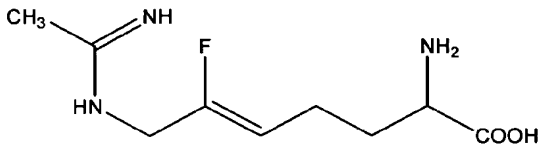
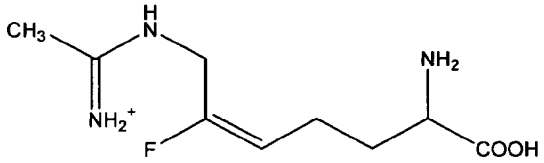
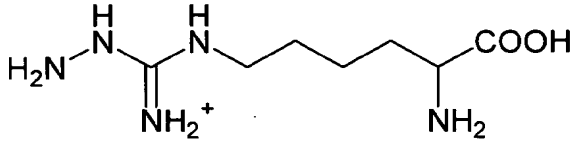




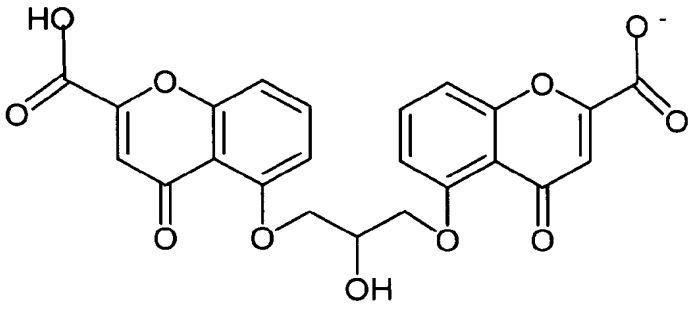


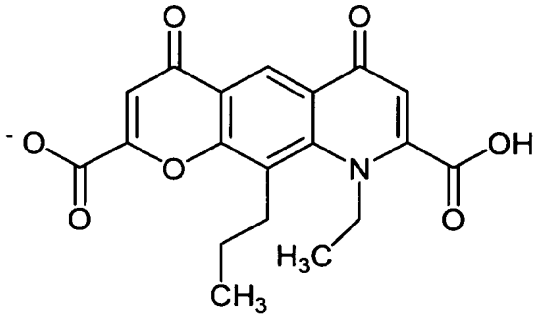


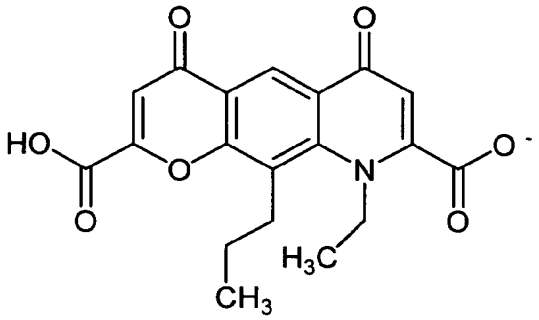


and their corresponding dications. Exemplary anions include:







and their corresponding dianions.

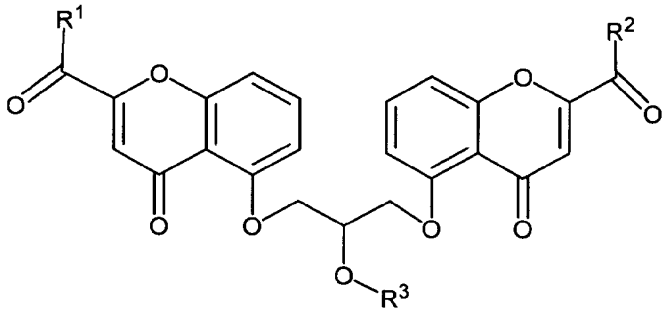
The invention also encompasses the salts themselves.

[0057] Combination therapy can be achieved by administering two or more agents, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so. Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them

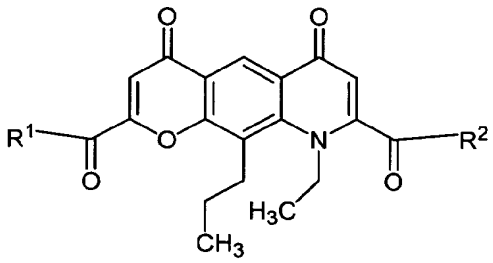
sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

[0058] The compounds of the present invention can be coadministered with any of the following: β-agonists (e.g. albuterol, formoterol, salmeterol), glucocorticoids (e.g. beclomethasone, budesonide, fluticasone), leukotriene antagonists (e.g. montelukast), and 5-lipoxygenase (e.g. zileuton).

[0059] Finally one may describe the compounds of formula I or II



I



II

in means-plus-function terms. In other words, -O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting iNOS;

-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is a chemical means for inhibiting iNOS;

-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is a chemical means for inhibiting iNOS.

Chemical means for inhibiting iNOS are compounds (i.e. chemicals) that exhibit IC_{50} below 25 μM when tested against human iNOS according to the method of Moore *et al.* J. Med. Chem. 39, 669-672 (1996). Examples of many such compounds are shown above. Preferred inhibitors are those with IC_{50} below 10 μM and most preferably below 5 μM. For the purpose of the invention, iNOS inhibitors should be selective for iNOS over eNOS and nNOS. Selective means having an IC_{50} against iNOS that is no more than $1/10^{th}$ the IC_{50} against nNOS and eNOS as measured by the method described in Moore (*op. cit.*) Unless some other meaning is clear from its context, the term "iNOS inhibitor", not further modified, as used herein refers to a selective iNOS inhibitor.

[0060] The compounds of the present invention may possess one or more of the following advantages: they lessen bronchial epithelial damage in asthma; they exhibit improved stability, formulation and manufacturing characteristics; they possess improved pharmacokinetic properties, allowing in many cases, once or twice daily inhaled dosing; they offer an alternative to steroid therapy

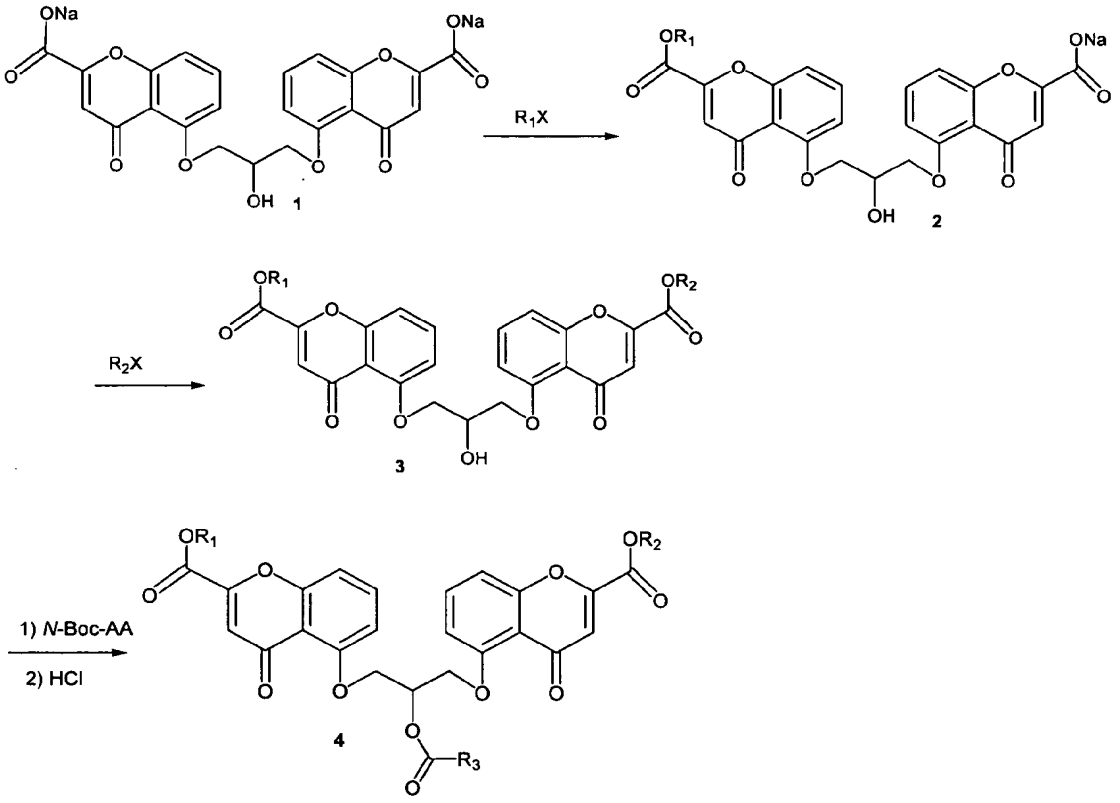
[0061] The efficacy of the compounds of the invention may be demonstrated in a test that measures airway hyperresponsiveness [see Muijsers *et al.* Br. J. Pharmacol. 134, 434 (2001) and Eynott *et al.* Eur. J. Pharm. 452, 123 (2002)] or in a test that measures inflammation in an airway [see Chen *et al.* Acta Pharmacol. Sin. 24, 697 (2003)].

[0062] In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants that are in themselves known, but are not mentioned here.

[0063] In Scheme I disodium chromylglycate **1** is treated with one equivalent of an alkyl halide in a dipolar aprotic solvent such as dimethylformamide (DMF) to provide the corresponding mono-ester **2**. Typically, this procedure also produces some diester **3**, wherein R1=R2 and unreacted **1**. After separation of the mono-ester **2** it can be converted into diester **3** by reaction with an alkyl halide in a dipolar aprotic solvent to

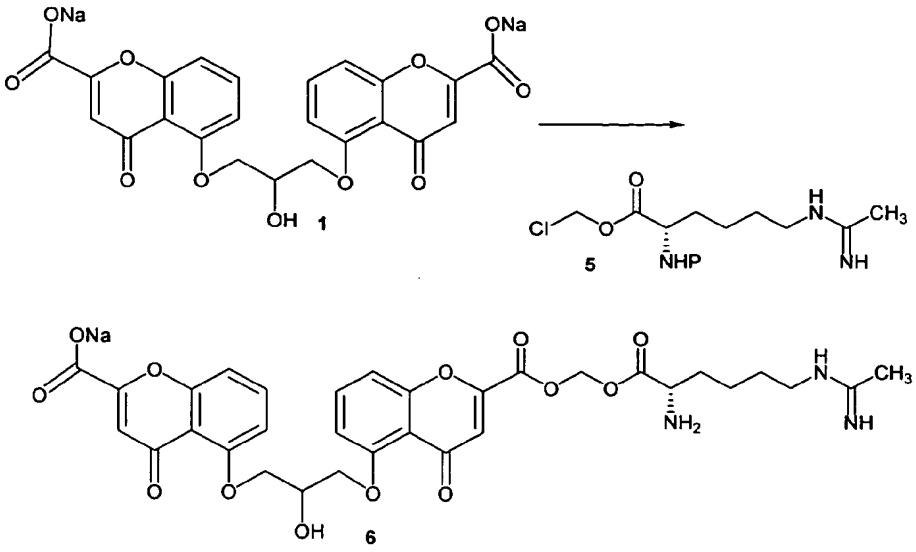
provide the diester **3**. The diester **3** is then condensed with an appropriately protected acid, such as an N-Boc-amino acid inhibitor of iNOS, in the presence of a dehydrating agent, such as 1,3-dicyclohexylcarbodiimide (DCC), to provide the protected ester. The protecting group is then removed to provide the desired chromyl iNOS inhibitors **4**. In the case of an N-Boc-amino acid, the protecting group can be removed by an acid such as HCl in dioxane.

Scheme I



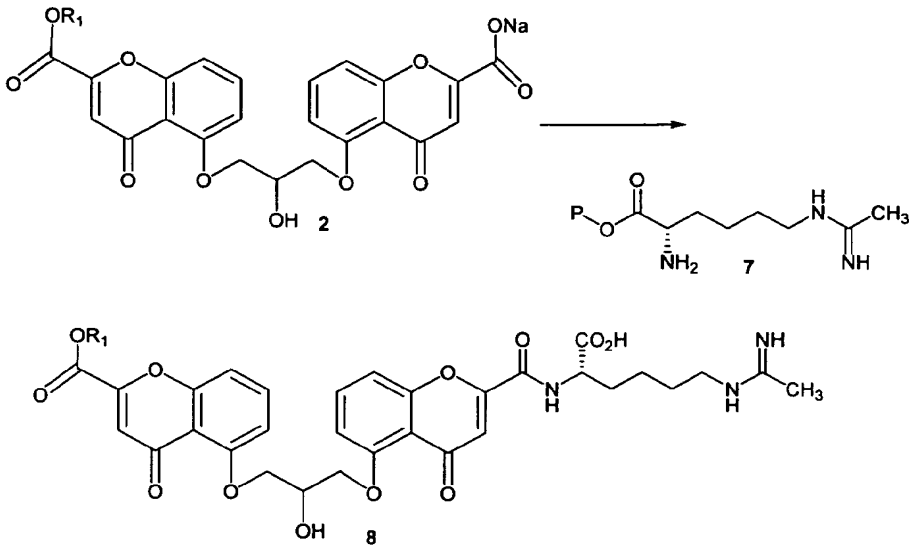
[0064] In Scheme II disodium chromylglycate **1** is treated with one equivalent the chloromethyl ester of a protected iNOS inhibitor such as **5** to provide, after purification, the corresponding ester. The ester is then deprotected to afford the desired chromyl iNOS inhibitor **6**.

Scheme II



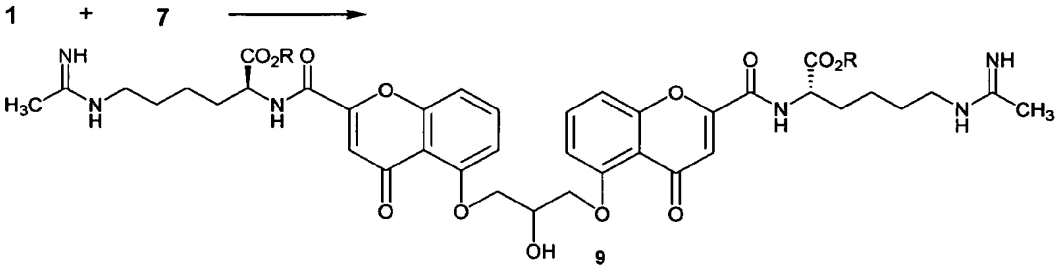
[0065] Scheme III illustrates the method for the preparation of mono-ester amide derivatives **8**. The route commences with the coupling of an orthogonally protected ester of an iNOS inhibitor **7** with the mono-ester **2** in the presence of a amide coupling agent such as 1,3-dicyclohexylcarbodiimide. The resulting amide derivative is then converted into the desired analogues **8** by removal of the ester of the iNOS moiety. The ester moiety of the iNOS inhibitor can be such things as the tert-butyl ester, the beta-trimethylsilylethyl ester, para-methoxybenzyl ester, and the like. If the iNOS inhibitor component does not possess an acid substituent then the amine can be coupled directly to **2** without the need for protection and deprotection. If the desired product is the free acid of **8** (R^1=H) the route can be to saponify the ester of **8**, or to couple one equivalent of the protected iNOS inhibitor **7** with **1** followed by removal of the protecting groups.

Scheme III



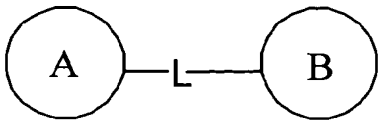
[0066] Illustrated in Scheme IV is the method used for the preparation of bis-iNOS amides of chromyln. The method involves coupling of **1** with the ester protected iNOS inhibitor moiety **7** in the presence of a dehydrating agent such as 1,3-dicyclohexylcarbodiimide to produce the ester protected version of **9**, R=ester. In a subsequent step the ester moiety is converted to the corresponding acid, **9**, R=H, by saponification. Suitable esters are those listed in Scheme III.

Scheme IV



The invention is characterized as follows:

[0067] An agent for treating a pulmonary disorder represented by the structure:



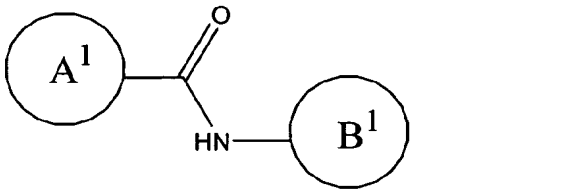
wherein

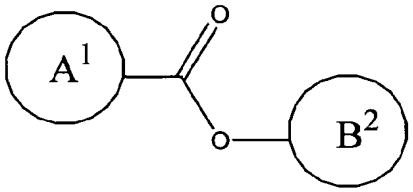
A is a mast-cell stabilizer;

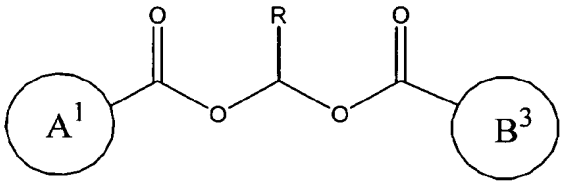
L is a covalent linkage;

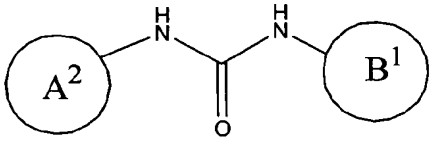
B is an iNOS inhibitor.

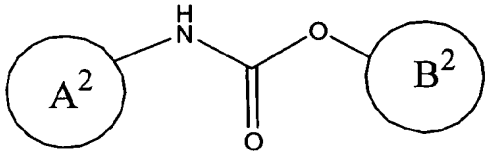
[0068] An agent according to paragraph [0067] wherein L is chosen from -CONH-, -COO-, -O(C=O)O-, -O(C=O)NH-, -NHCONH- and -(C=O)OCH(R)O(C=O)- and the compound is represented by a structure chosen from:

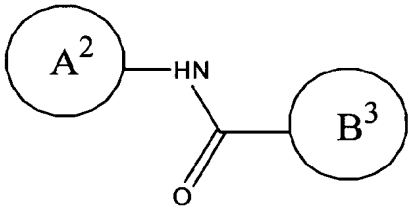


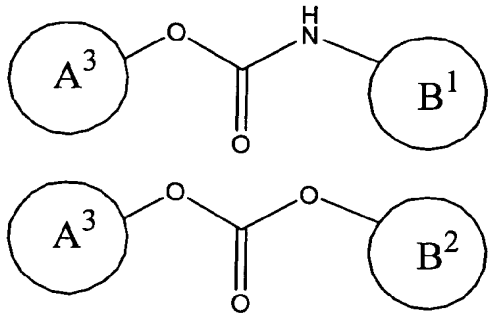


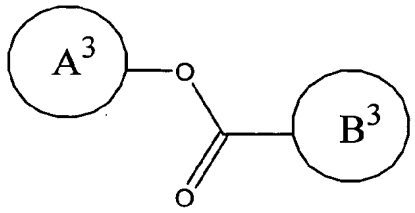












and

wherein

A^1 is a mast-cell stabilizer having a carboxylic acid substituent;

A^2 is a mast-cell stabilizer having an amine substituent;

A^3 is a mast-cell stabilizer having an alcohol substituent;

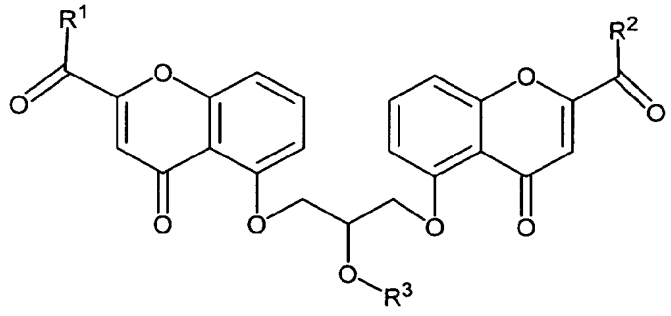
B^1 is an iNOS inhibitor having an amine substituent;

B^2 is an iNOS inhibitor having an alcohol substituent;

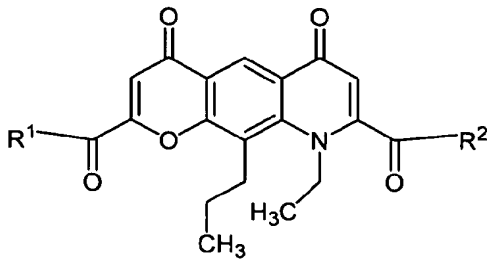
B^3 is an iNOS inhibitor having a carboxylic acid substituent; and

R is hydrogen or methyl.

[0069] A compound of formula I or II



I



II

wherein

R^1 and R^2 are chosen from hydroxy, alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -$O^- X^+$, wherein X^+ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

-O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of iNOS;

R^5 is -O-R^{20}-U, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

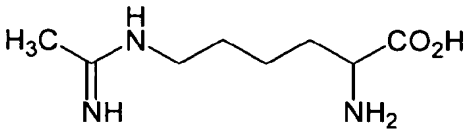
-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is an inhibitor of iNOS;

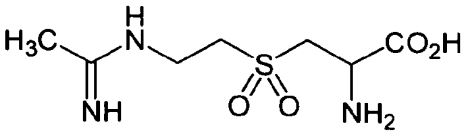
-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is an inhibitor of iNOS;

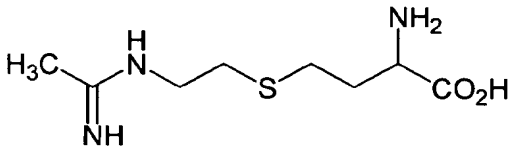
G is a linking moiety cleavable under physiologic conditions; and

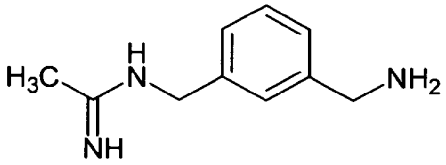
at least one of R^1, R^2 and R^3 must be -G-O(C=O)R^4, -NHR^6, -OR^7, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 or -(C=O)OR^7.

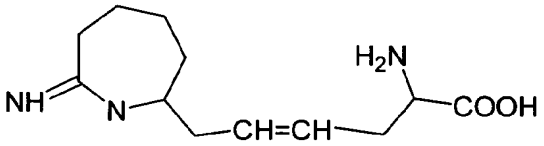
[0070] A compound according to paragraph **[0068]** wherein R^4COOH and R^6NH_2 are chosen from:

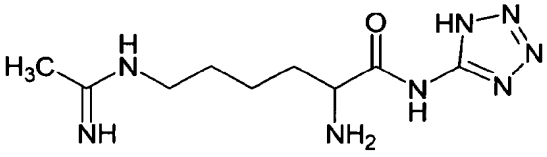


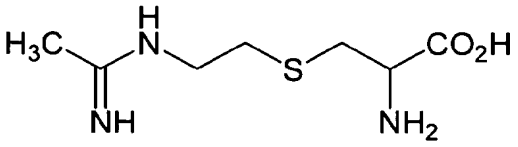


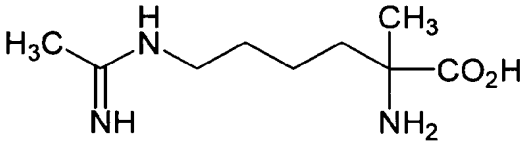


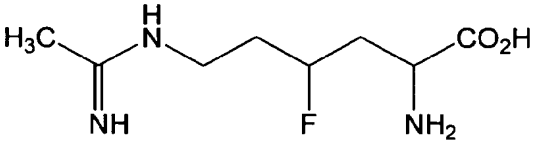


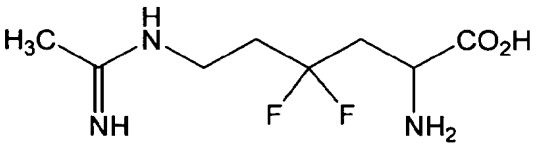


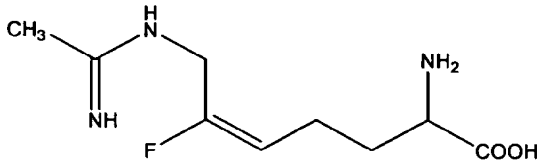


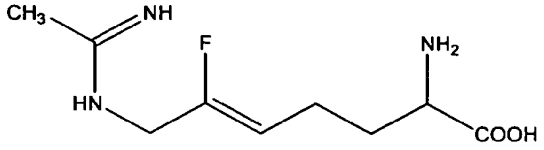


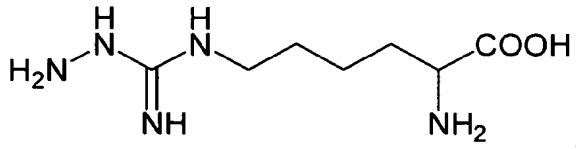




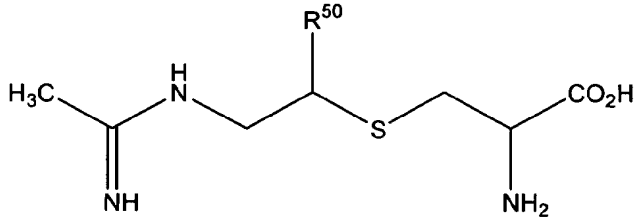






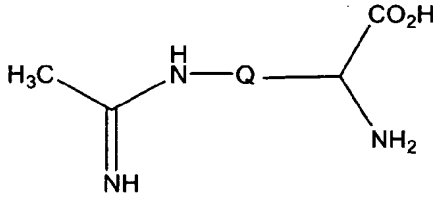
and 

[0071] A compound according to paragraph **[0069]** wherein R^4COOH and R^6NH_2 are chosen from compounds of structure:



wherein R^{50} is chosen from C_1 to C_4 alkyl, C_3 to C_4 cycloalkyl, C_1 to C_4 hydroxyalkyl and C_1 to C_4 haloalkyl.

[0072] A compound according to paragraph **[0069]** wherein R^4COOH and R^6NH_2 are chosen from compounds of structure:



wherein Q is chosen from $-CH_2CH=CHCH_2-$, $-(CH_2)_pX(CH_2)_q-$, -O- , $-NR^{51}-$ and $-(CH_2)_rA(CH_2)_s-$;

p is 2 or 3;

q is 1 or 2;

X is $S(O)_x$;

x is 0, 1 or 2;

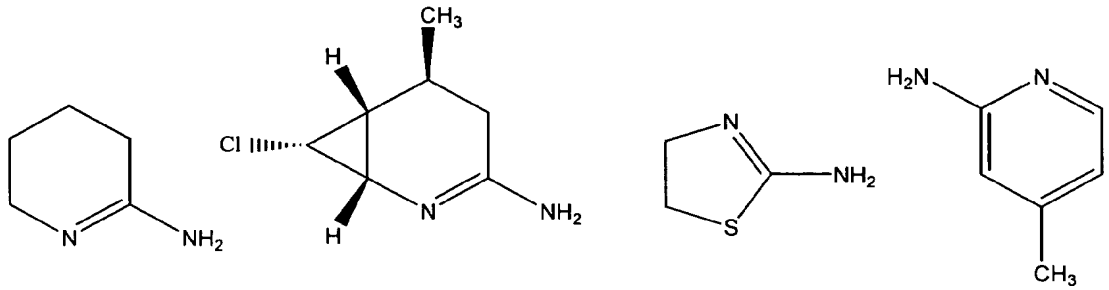
R^{51} is H or C_{1-6} alkyl;

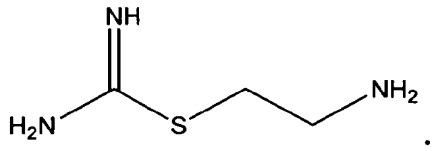
r is 1 or 2;

s is 1 or 2; and

A is cyclobutyl, phenyl or pyridyl.

[0073] A compound according to paragraph **[0069]** wherein R^6NH_2 is chosen from compounds of structure:



and  .

[0074] A compound according to paragraph **[0069]** wherein

R^1 and R^2 are chosen from hydroxy, alkoxy, $-R^5$, $-NHR^6$, $-OR^7$ and $-O^- X^+$; and

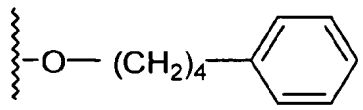
R^3 is chosen from hydrogen, $-(C=O)R^4$, $-(C=O)R^5$, $-(C=O)NHR^6$ and $-(C=O)OR^7$.

[0075] A compound according to paragraph **[0069]** wherein at least one of

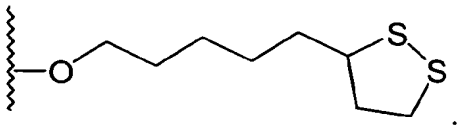
R^1, R^2 and R^3 is $-G-O(C=O)R^4$ or $-(C=O)-G-O(C=O)R^4$; and

G is chosen from $-OCH_2-$ and $-OCH(CH_3)-$.

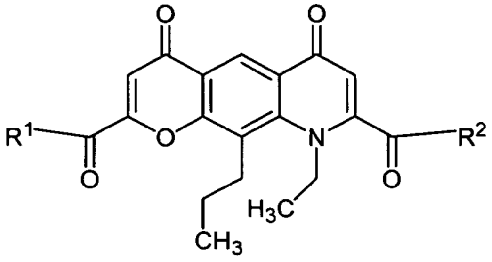
[0076] A compound according to any of paragraphs **[0069]** to **[0075]** wherein R^5 is



[0077] A compound according to any of paragraphs **[0069]** to **[0075]** wherein R^5 is



[0078] A compound of formula II according to paragraph **[0069]**:



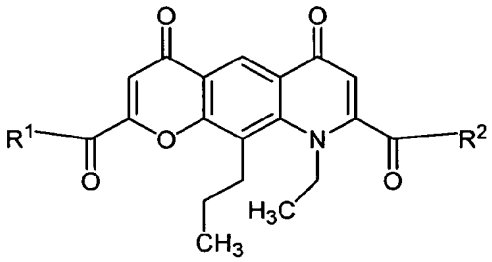
II

wherein

R^1 is chosen from hydroxy, R^5 and $-O^- X$;

R^2 is chosen from $-G-O(C=O)R^4$, $-NHR^6$ and OR^7.

[0079] A compound of formula II according to paragraph **[0069]**:



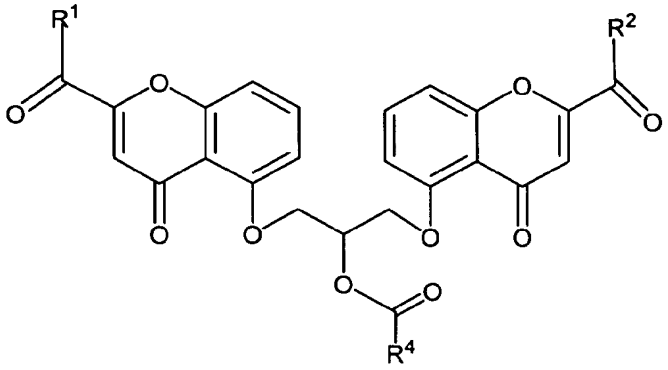
II

wherein

R^1 is chosen from $-G-O(C=O)R^4$, $-NHR^6$ and OR^7; and

R^2 is chosen from hydroxy, R^5 and $-O^- X$.

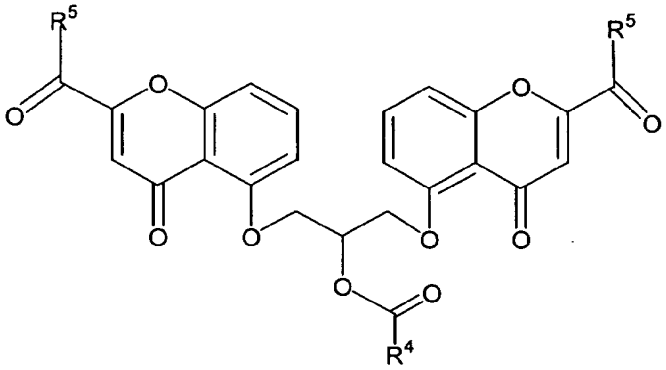
[0080] A compound according to paragraph **[0069]** of formula



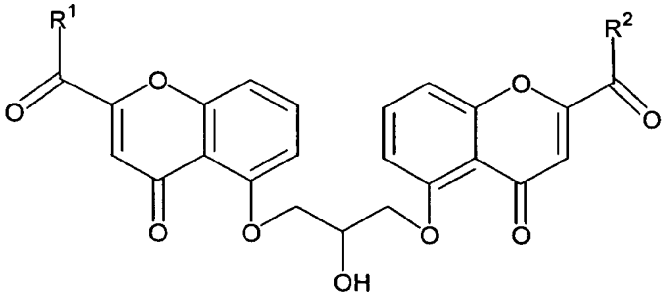
wherein

R^1 and R^2 are chosen from hydroxy, alkoxy and $-O^- X^+$.

[0081] A compound according to paragraph **[0069]** of formula



[0082] A compound according to paragraph **[0069]** of formula:



wherein

R^1 is chosen from $-G-O(C=O)R^4$, $-NHR^6$ and OR^7 ; and

R^2 is chosen from hydroxy, alkoxy, R^5 and $-O^- X$.

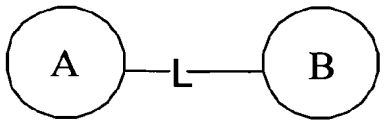
[0083] A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of paragraphs **[0067]** to **[0082]**.

[0084] An aerosol pharmaceutical composition according to paragraph **[0083]**.

[0085] An oral pharmaceutical composition according to **[0083]**.

[0086] An oral pharmaceutical composition according to paragraph **[0085]** in the form of a tablet, capsule or syrup.

[0087] A method for treating a pulmonary disorder comprising administering a compound represented by the structure:



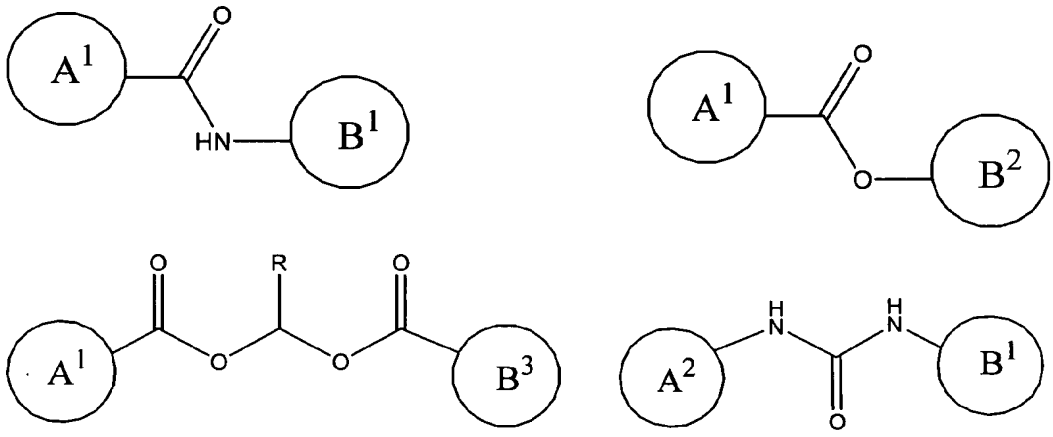
wherein

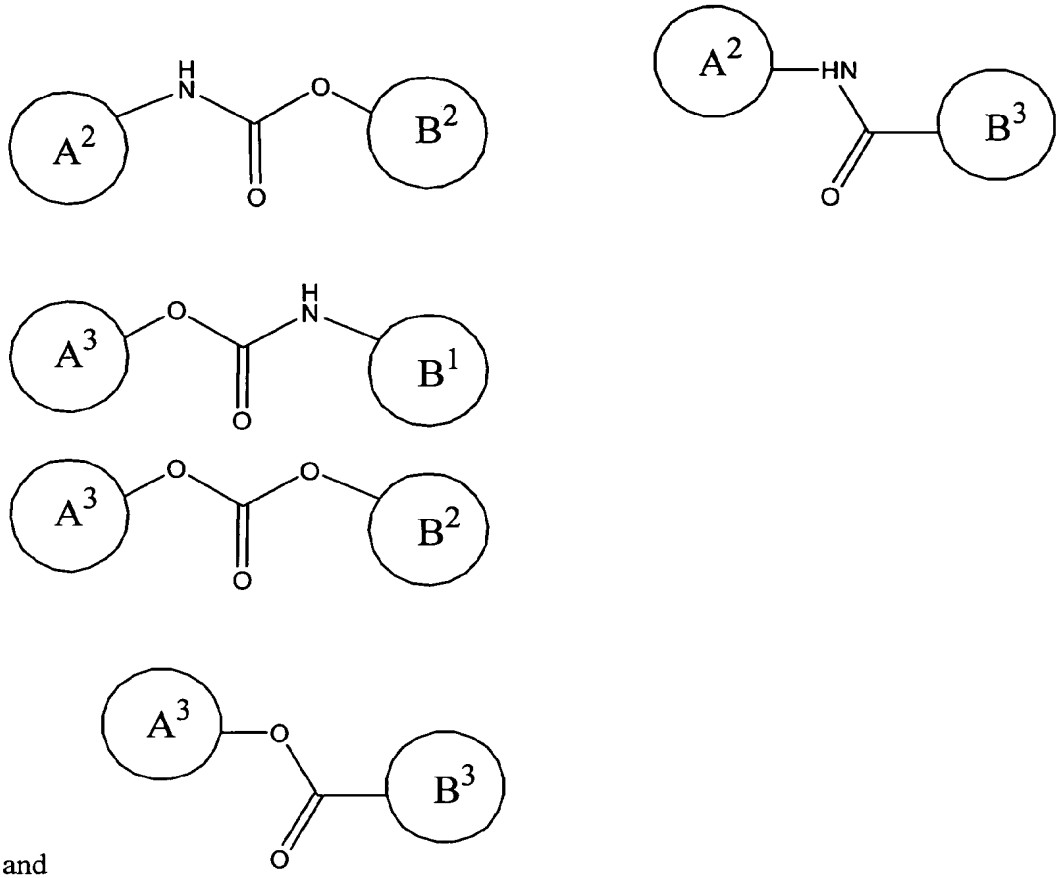
A is a mast-cell stabilizer;

L is a covalent linkage;

B is an iNOS inhibitor.

[0088] A method according to paragraph **[0087]** for treating a pulmonary disorder wherein L is chosen from -CONH-, -COO-, -O(C=O)O-, -O(C=O)NH-, -NHCONH- and -(C=O)OCH(R)O(C=O)- and the compound is represented by a structure chosen from:





and

wherein

A^1 is a mast-cell stabilizer having a carboxylic acid substituent;

A^2 is a mast-cell stabilizer having an amine substituent;

A^3 is a mast-cell stabilizer having an alcohol substituent;

B^1 is an iNOS inhibitor having an amine substituent;

B^2 is an iNOS inhibitor having an alcohol substituent;

B^3 is an iNOS inhibitor having a carboxylic acid substituent; and

R is hydrogen or methyl.

[0089] A method for treating a pulmonary disorder comprising administering a compound according to any of paragraphs **[0069]** to **[0082]**.

[0090] A method according to paragraphs **[0087, 0088]** or **[0089]** for treating bronchospasm.

[0091] A method according to **[0087, 0088]** or **[0089]** for inducing bronchodilation.

[0092] A method according to **[0087, 0088]** or **[0089]** for treating chronic obstructive pulmonary disease.

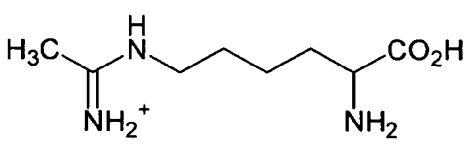
[0093] A method according to **[0087, 0088]** or **[0089]** for treating asthma..

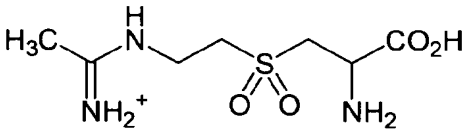
[0094] A method according to **[0087, 0088]** or **[0089]** for treating rhinitis.

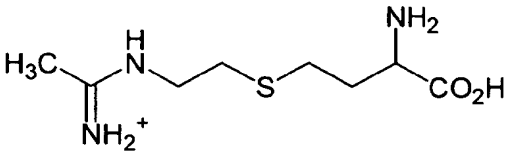
[0095] A method according to **[0087, 0088]** or **[0089]** wherein the pulmonary disorder is acute pulmonary vasoconstriction, pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, hypoxia, chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension, primary pulmonary hypertension or chronic hypoxia.

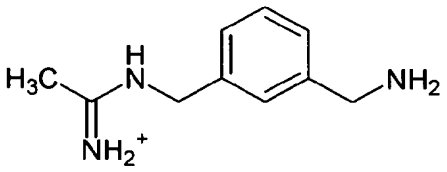
[0096] A method for treating a pulmonary disorder comprising co-administering a mast-cell stabilizer and an iNOS inhibitor in the form of a salt, in which one of said mast-cell stabilizer and said iNOS inhibitor is a cation or dication, and the other of said mast-cell stabilizer and said iNOS inhibitor is an anion or dianion.

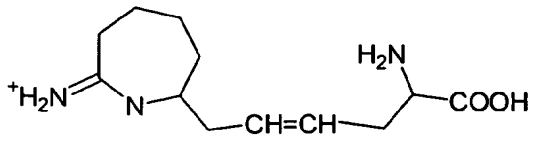
[0097] A method according to paragraph **[0096]** wherein said cation is chosen from:

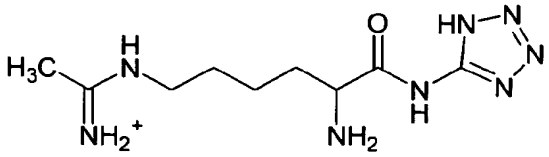


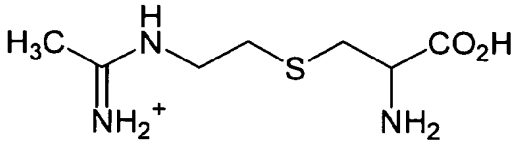


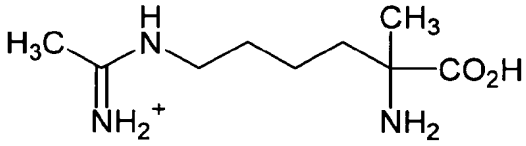


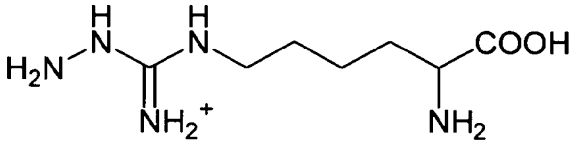


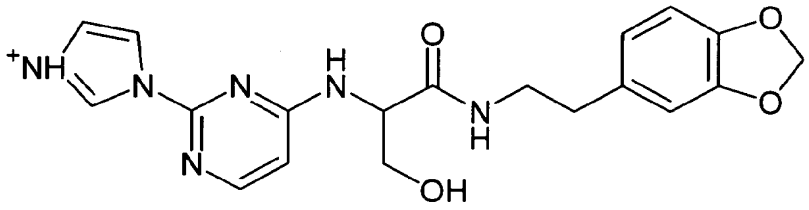


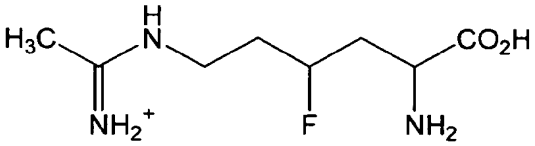


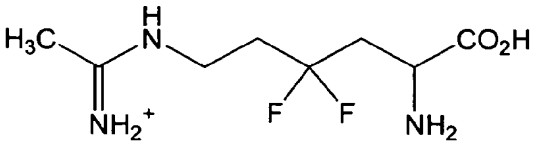


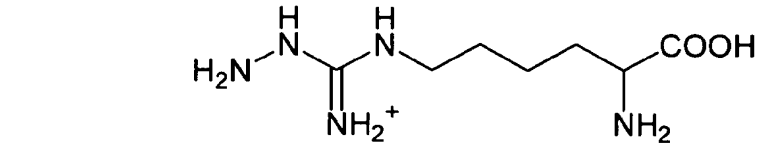


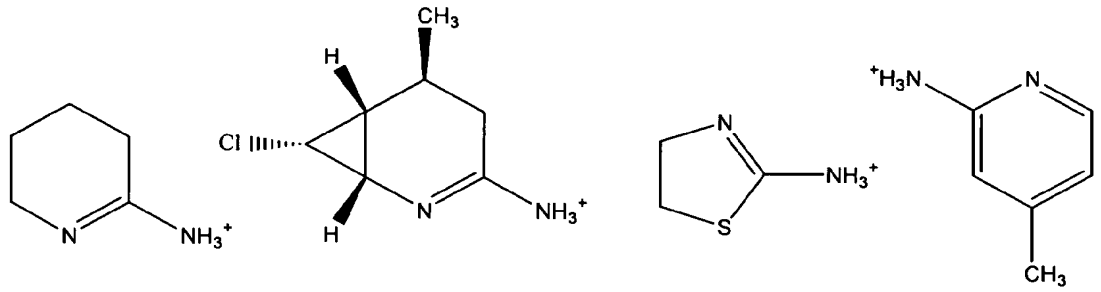


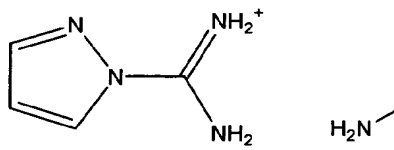


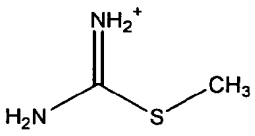


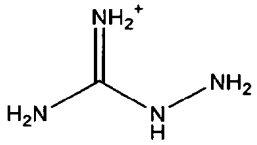


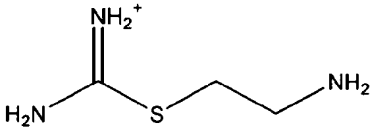


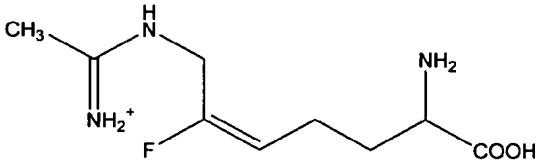


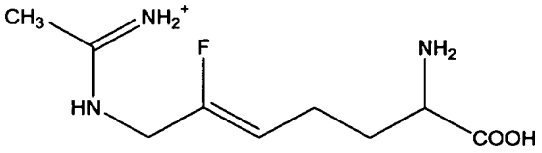


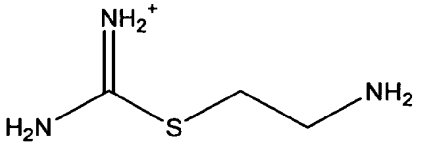


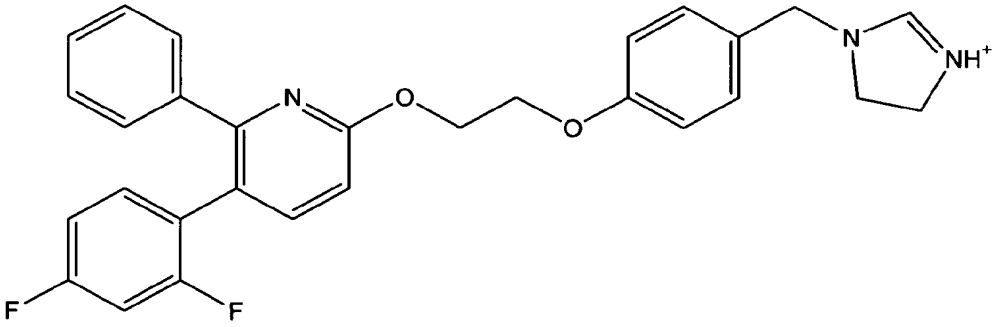






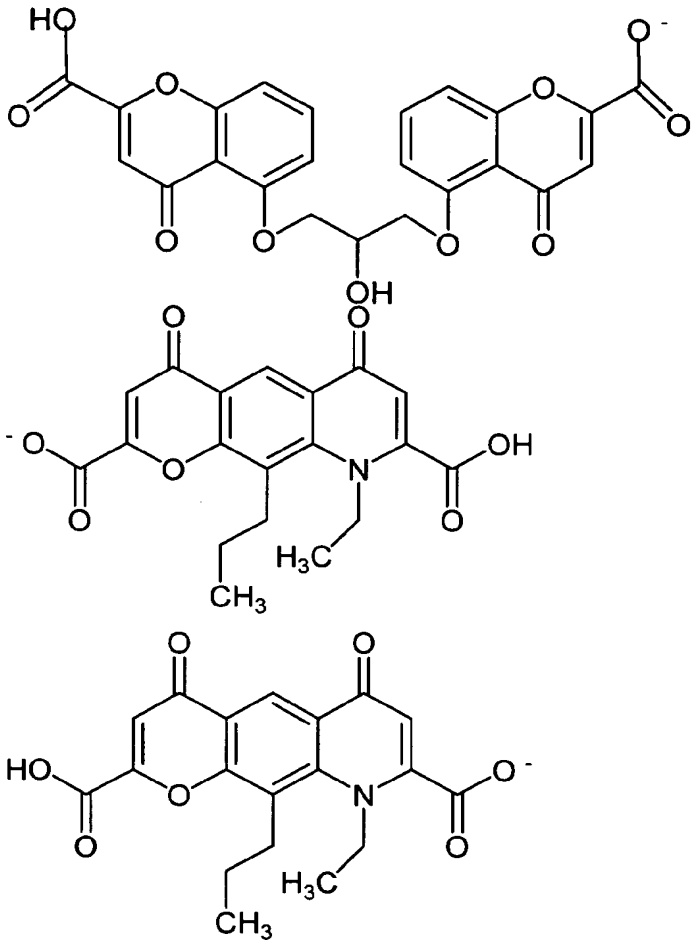






and their corresponding dications;

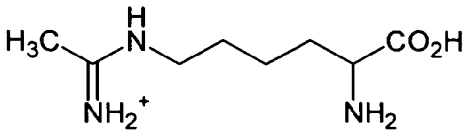
and said anion is chosen from:

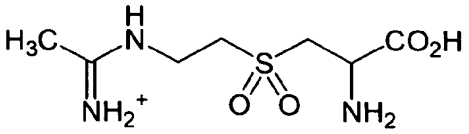


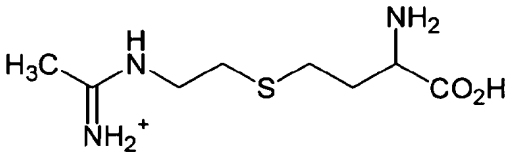
and their corresponding dianions.

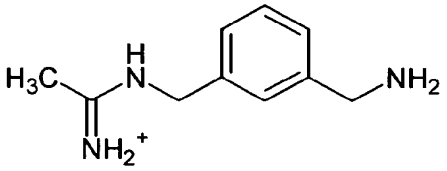
[0098] A salt comprising a mast-cell stabilizer and an iNOS inhibitor wherein one of said mast-cell stabilizer and said iNOS inhibitor is a cation or dication, and the other of said mast-cell stabilizer and said iNOS inhibitor is an anion or dianion.

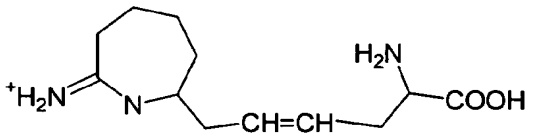
[0099] A salt according to paragraph **[0098]** wherein said cation is chosen from:

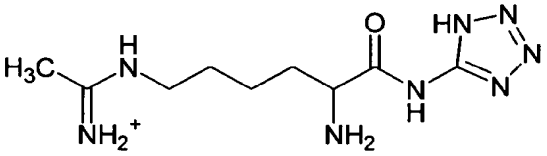


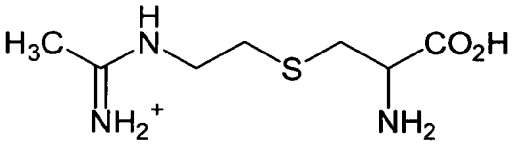


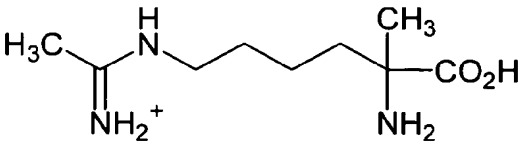


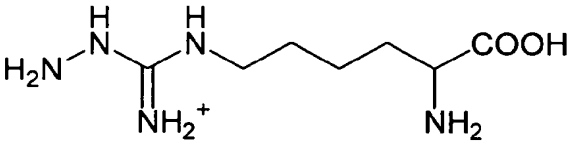


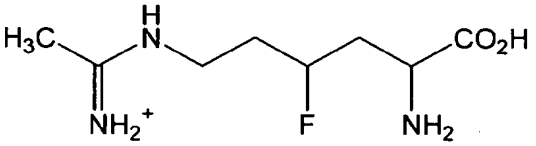


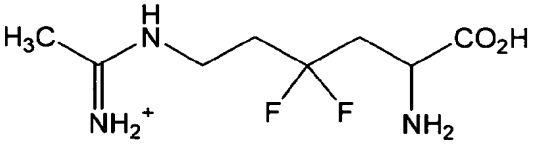


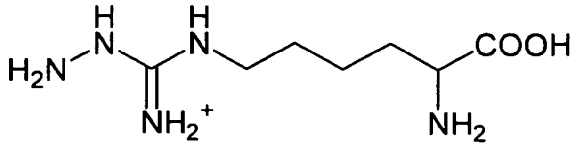


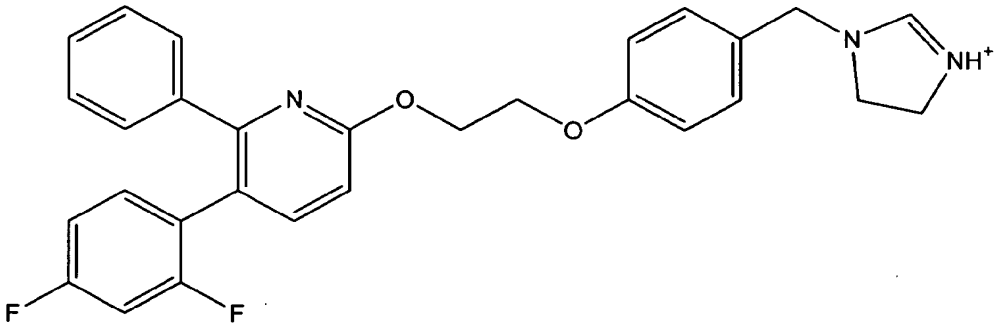


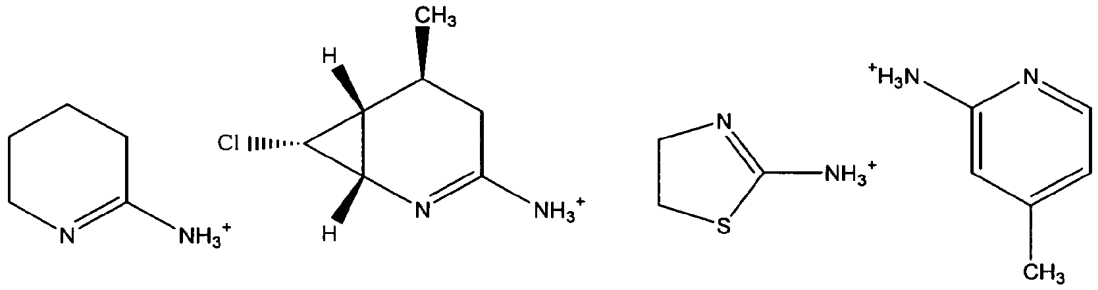


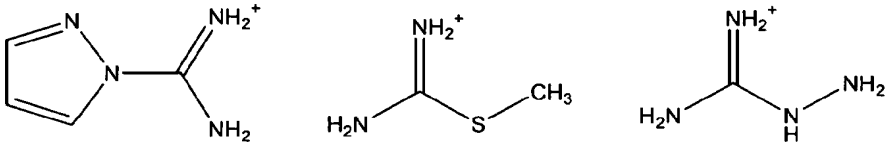


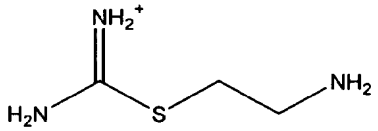


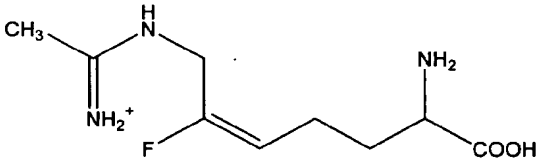


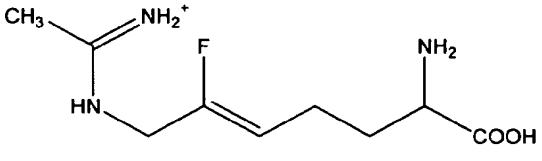




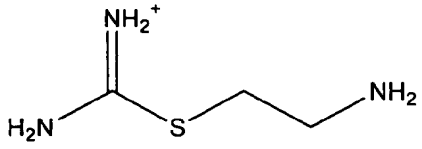






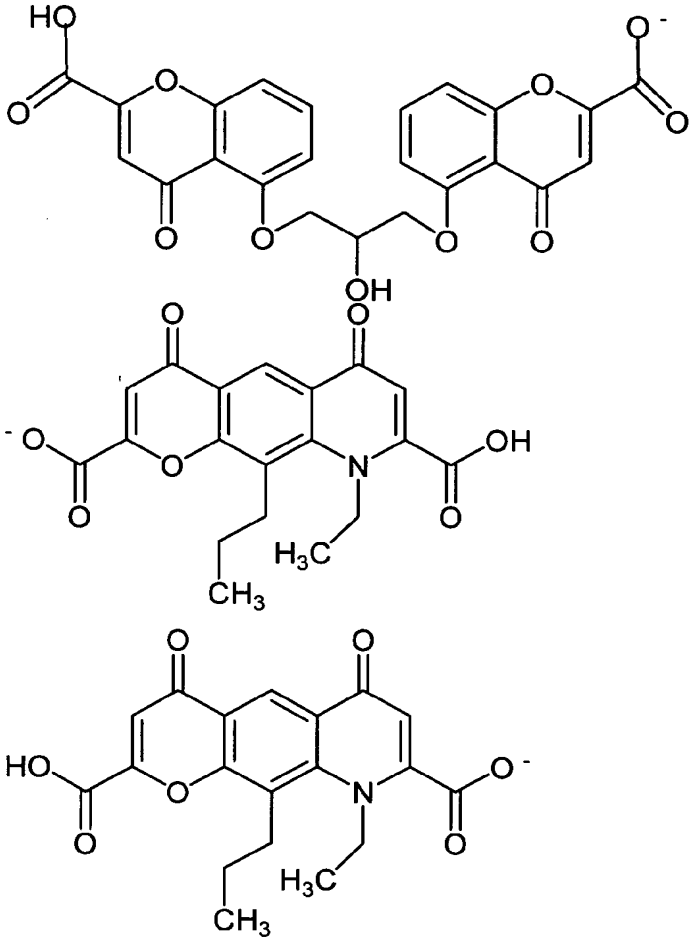


and



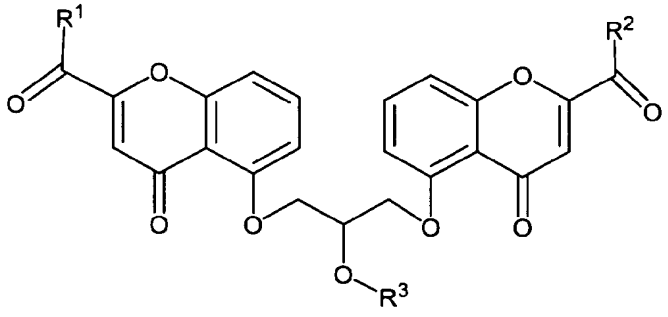
and their corresponding dications;

and said anion is chosen from:

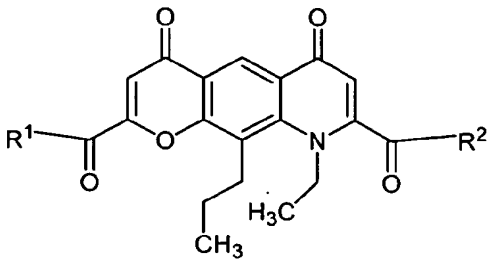


and their corresponding dianions.

[00100] A compound of formula I or II



I



II

wherein

R^1 and R^2 are chosen from hydroxy, alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -$O^- X^+$, wherein X^+ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

-O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting iNOS;

R^5 is -O-R^{20}-U, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is a chemical means for inhibiting iNOS;

-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is a chemical means for inhibiting iNOS;

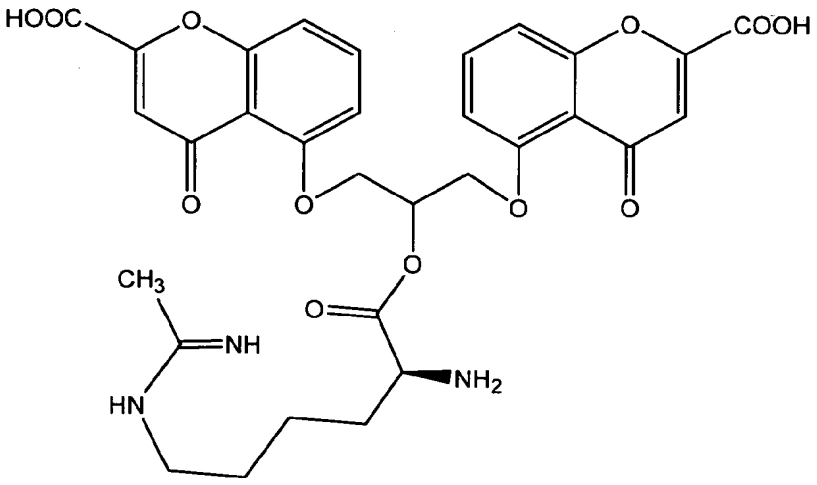
G is a linking moiety cleavable under physiologic conditions; and

at least one of R^1, R^2 and R^3 must be -G-O(C=O)R^4, -NHR^6, -OR^7, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 or -(C=O)OR^7.

COMPOUNDS AND METHODS FOR THE TREATMENT OF ASTHMA

Abstract of the Disclosure

[00101] Compounds and methods for the treatment of asthma are disclosed. The methods involve mast cell stabilization together with selective inhibition of iNOS. The compounds are combinations of a mast cell inhibiting moiety and an inhibitor of iNOS. An example is:



APPLICATION DATA SHEET

Electronic Version v14
Stylesheet Version v14.0

Title of Invention	COMPOUNDS AND METHODS FOR THE TREATMENT OF ASTHMA

Application Type: provisional, utility

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Customer Number: 23405 *23405*

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